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"*In Silico* Molecular Docking Studies of Alzheimer's Disease Targets and Bioactive Compounds"

Pre- Synopsis Submitted
For the Confirmation of the Ph.D. Topic

In the Subject

'Bioinformatics'

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1) INTRODUCTION

Alzheimer's disease (AD) is most common neurodegenerative disorder.[1] It accounts for 60 % - 70%of all cases of dementia which is the fifth leading cause of death worldwide.[2] No a days, there is no effective therapies to stop or reverse the AD disease therefore a lot of studies are focused on preventative methods of AD. Proper diet with essential nutrients is necessary for older people to reduce risk factor of AD. Nutrition is one of the primary lifestyle factors influencing the risk of AD, and previous research has indicated that its preventive potential can be related to bioactive compounds derived from different food products. [3] Several studies have suggested that healthy nutrition is one of the primary lifestyle factors that could reduce the risk of AD. [4,5,6] A recent studies show that bioactive compounds derived from well- balanced healthy diet reduces the risk factors of AD.[7] A well balanced diet can provide neuro protection, which indicates that bioactive compounds could influences the underlying mechanism of AD development. The behavioral changes observed in AD are manifestations. Of underlying processes affecting the Central Nervous System. [8]

Alzheimer's disease is a life-threatening neurodegenerative disorder. About 50 million people across the globe are affected by this disease.[9] At final stages, this disease causes patients to lose cognitive ability, memory, and brain cells to the point of being totally dependent on other individuals for livelihood. The incidence of this disease is increasing across the world in the recent years, making the need of a better drug urgency. Existing drugs show various side effects and natural sources of medicinal drugs are being explored. In this study, we explore the activity of natural compounds isolated through Molecular Docking tools.

As per the cholinergic hypothesis, AChE and BChE hydrolytic enzymes detected in neurofibrillary tangles and neurotic plaques in the brain, act on ACh and Butyrylcholine to terminate its actions in the synaptic cleft by cleaving the neurotransmitter to choline and acetate. [10] It was suggested that AChE predominated in the healthy brain, whereas BChE considered playing a minor role in regulating brain ACh levels. However, BChE activity progressively increases in patients with AD, while AChE activity remains unchanged or declines.

A typical process observed in AD is the accumulation of amyloid beta forms aggregates known as senile plaques & is a short peptide produced from naturally occurring amyloid precursor protein

(APP)Under physiological conditions amyloid beta performs important regulatory functions plays a role in axonal growth & influences synaptic plasticity.[11]

Recent medication available for the treatment on AD is Donepezil, Rivastigmine, Galantmine, Memantine etc.[5]

- Donepezil- Donepezil is Cholinesterase inhibitor treats mild, moderate & severe AD by preventing the breakdown of acetylcholine in brain region.
- Rivastigmine – It is also Cholinesterase inhibitor prevent AD by breakdown of Acetylcholine & butyrylcholine.
- Galantamine - It is Cholinesterase inhibitor treats mild, moderate & severe AD by preventing the breakdown of acetylcholine & nicotinic receptors to release more acetylcholine in the brain.
- Memantine – memantine is NMDA antagonist treats moderate to severe AD by blocking the toxic effects associated with excess glutamate & regulates glutamate activation.
- Memantine & Donepezil (Combination) – It is also NMDA antagonist which blocks the toxic effects associated with excess glutamate & prevents the breakdown of acetylcholine in the brain region.

The major side effects of above medicines includes Headache , Nausea, Vomiting, Diarrhea, Dizziness, Anorexia etc.

Pharmaceutical companies, though very much interested in well-established pharmacology and chemistry based drug discovery approaches, are facing various complications in finding novel drugs Now-a-days, the pharmaceutical companies make huge investments for development of new drugs. At this juncture, Bioinformatics has emerged into pharmacology to fulfill the aspiration of pharmacologists to generate several potential drugs in short period with low risk

The major application is computer aided drug design, in which structure-based drug design (SBDD) plays a very important role in identification of new drugs against the selected therapeutic targets.[12] SBDD requires knowledge on biological therapeutic target, aims to discover small molecules (ligands) with desired chemical or drug properties. This approach provides an idea regarding interaction of target and ligands by creating biological environment computationally.

2) REVIEW OF LITERATURE

- **Maurer U, Maurer K (2003) -** The ancient Greek and Roman philosophers and physicians associated old age with increasing dementia It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as Alzheimer's disease, named after him, in a fifty-year-old woman he called Auguste D. He followed her case until she diedin 1906 when he first reported publicly on it.
- **Tackenberg C, Kulic L, Nitsch RM (2020) -** Alzheimer's disease is believed to occur when abnormal amounts of amyloid beta (Aβ), accumulating extracellular as amyloid plaques and tau proteins, or intracellular as neurofibrillary tangles, form in the brain, affecting neuronal functioning and connectivity, resulting in a progressive loss of brain function.
- **Rithvik Ganesh & Iyanar Kannan,** (2017)Biomedical & Pharmacology Journal Vol.(3), 1489-1494 Alzheimer's disease is a deadly form of dementia, and can greatly affect the way a person can think and behave. It is the sixth leading cause of death in the US alone. Clusters of Beta-Amyloid (Plaques) and twisted tangles of a protein called Tau (Tangles) are the primary cause of Alzheimer's disease, as noted by Alois Alzheimer in 1906. Plaques and Tangles can block cell-to-cell signaling and disintegrate the cell transport system. The 3-dimensional structure of three drug targets, Betasecretase 1, Cholinesterase, and Tau Protein kinase were retrieved from the RCSB PDB database. A total of 150 derivatives of Curcumin.
- **Pedro H. M. Torres,[1] Ana C. R. Sodero,[2] Paula Jofily,[3] and Floriano P. Silva-Jr[4],** Molecular docking has been widely employed as a fast and inexpensive technique in the past decades, both in academic and industrial settings. Although this discipline has now had enough time to consolidate, many aspects remain challenging and there is still not a straightforward and accurate route to readily pinpoint true ligands among a set of molecules, nor to identify with precision the correct ligand confirmers within the binding pocket of a given target molecule.
- **Jason Tom Abraham, H.Noorul Samsoon Maharifa, S.Hemalatha (2022)** The incidence of this disease is increasing across the world in the recent years, making the need of a better drug urgency. Existing drugs show various side effects and natural sources of medicinal drugs are being explored

3) OBJECTIVES OF RESEARCH

- To screen the bioactive compounds from Natural origin.
- To identify the drug targets in Alzheimer disease.
- To predict the molecular descriptors properties of Bioactive compounds.
- To calculate the Binding free energy of docked confirmers.
- To Predict the ADMET properties of selected Bioactive compounds

4) METHODOLOGY

To screen bioactive compounds from natural sources, the following approach can be adopted.

1. **Data Collection**: Gather information on bioactive compounds from natural sources such as medicinal plants, marine organisms, fungi, and other natural products. Established databases, scientific literature, and traditional medicine resources can serve as valuable sources of information.

2. **Compound Selection**: Select a diverse set of bioactive compounds based on their reported medicinal properties, ethnopharmacological knowledge, and relevance to Alzheimer's disease. Consider compounds with anti-inflammatory, antioxidant, neuroprotective, and cholinesterase inhibitory activities, as these are often associated with potential therapeutic effects against AD.

3. **Database Search**: Utilize various databases and online resources to search for bioactive compounds from natural sources. Examples include PubChem, ChEMBL, Herbal Medicine Databases, and Marine Natural Products Databases. These databases provide comprehensive information on the chemical structures, biological activities, and sources of the compounds.

4. **Molecular Descriptors and ADME Filtering**: Employ computational tools to calculate molecular descriptors such as molecular weight, hydrogen bond donors/acceptors, lipophilicity (logP), and other physicochemical properties. Apply filters based on drug-likeness criteria and absorption, distribution, metabolism, and excretion (ADME) properties to prioritize compounds with favorable pharmacokinetic profiles.[13]

5. **Pharmacophore Modeling**: Generate pharmacophore models using computational techniques to identify common features shared among known bioactive compounds. These models can aid in the virtual screening of natural compound databases, highlighting potential compounds that fit the defined pharmacophoric features.

6. **Virtual Screening**: Employ docking simulations or ligand-based virtual screening techniques to evaluate the binding affinity and interactions of the selected bioactive compounds against key Alzheimer's disease targets such as BACE-1, AChE, and tau protein. Use molecular docking software (e.g., AutoDock, Vina) or ligand-based methods (e.g., molecular fingerprints, shape-based similarity) to prioritize compounds based on their predicted binding affinity.

7. **Validation and Experimental Studies**: Shortlist the top-ranking bioactive compounds from the virtual screening and perform experimental studies to validate their activity against Alzheimer's disease targets. Techniques such as in vitro assays, cellular models, and animal models can be utilized to assess the compounds' efficacy, safety, and mechanism of action.

By following this screening approach, researchers can identify potential bioactive compounds from natural sources that show promising interactions with Alzheimer's disease targets. This approach combines computational methods with experimental validation, facilitating the discovery of novel natural compounds for future drug development or as leads for further optimization.

Use of following Molecular Docking tools

- **Autodock** – Develop by Morris & co-workers, The Scripps Research Institute.
- **GOLD -** Developed by Cambridge Crystallographic Data Centre (CCDC).
- **DOCK –** Developed by University of California, San Francisco**..**
- **SANJEEVINI –** Developed by IIT Delhi
- **GemDock –** (Generic Evolutionary Method for Molecular Docking) Developed by Jinn – Moon Yang, a Professor of the Institute of Bioinformatics Taiwan
- **Hex Protein Docking –** University of Aberdeen UK
- **GRAMM –** (Global Range Molecular Matching)
- **Protein Docking –** A Center for Bioinformatics, University of Kansas.
- **FlexX –** T.Lengauer & Rarey
- **Glide –** Schrodinger LLC.
- **Patchdock –** Dina Schneidman- Duhovny, Yuval Inbar, Ruth Nussinov & Haim J. Wolfson.
- With the help of above Molecular docking tools we can analysis the bioactive compounds by following steps.[15]
  1) Target / Receptor selection and preparation.
  2) Ligand selection and preparation.
  3) Docking with various Molecular Docking tools.
  4) Evaluating docking results.

5) IMPORTANCE OF STUDY

- Drug discovery requires two main methods: virtual computational screening techniques and traditional experimental high-throughput methods. Molecular docking is an established computational structure-based method used in drug discovery. It allows the identification of potential drug targets and predicting molecular ligand-target interactions at the atomic level. Hence, the behavior of the molecules at the binding site as well as the biochemical processes can be characterized.
- Alzheimer's disease is a life-threatening neurodegenerative disorder. About 50 million people across the globe are affected by this disease. At final stages, this disease causes patients to lose cognitive ability, memory, and brain cells to the point of being totally dependent on other individuals for livelihood. The incidence of this disease is increasing across the world in the recent years, making the need of a better drug urgency. Existing drugs show various side effects and natural sources of medicinal drugs are being explored. In this study, we explore the activity of natural compounds isolated through Molecular Docking tools.
- Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain, leading to cognitive decline and memory impairment. Despite extensive research, effective treatments for AD remain elusive. In recent years, in silico molecular docking studies have emerged as a valuable tool for identifying potential therapeutic compounds by predicting their binding affinity to specific disease targets.
- With the predictions from molecular docking, the ligand can then be synthesized and tested experimentally. The binding complex can be crystallized to further understand the binding mechanism, as well as potential inhibitors. This saves time and money compared to traditional high-throughput methods where a vast number of ligands were screened experimentally. Molecular docking provides a more refined, target-based method for drug discovery.
- Now-a-days, the pharmaceutical companies make huge investments for development of new drugs. At this juncture, Bioinformatics has emerged into pharmacology to fulfill the aspiration of pharmacologists to generate several potential drugs in short period with low risk

- This research aims to employ in silico molecular docking [14] techniques to investigate the interactions between bioactive compounds and key molecular targets implicated in Alzheimer's disease. The study will utilize computational models and algorithms to analyze the binding patterns and affinities of selected bioactive compounds against targets such as beta-secretase (BACE-1), acetylcholinesterase (AChE), and tau protein.
- The methodology will involve the collection of bioactive compounds with known pharmacological activities from established databases and literature. These compounds will be docked against the three selected targets using state-of-the-art docking software. The docking simulations will allow the prediction of binding modes and the calculation of binding energies to evaluate the strength of interactions.
- Furthermore, the study will employ molecular dynamics simulations to assess the stability and dynamics of the protein-ligand complexes over time. These simulations will provide insights into the flexibility of the binding site and the strength of the ligand-protein interactions under dynamic conditions.
- The findings from this research will contribute to the identification and prioritization of potential bioactive compounds with promising therapeutic potential for Alzheimer's disease. By utilizing in silico techniques, the study aims to accelerate the process of drug discovery and provide a cost-effective approach for screening and selecting lead compounds for further experimental validation.
- Overall, this investigation seeks to bridge the gap between computational predictions and experimental validations by providing valuable insights into the binding interactions between bioactive compounds and Alzheimer's disease targets. Ultimately, these findings may aid in the development of novel therapeutics or repurposing of existing drugs to combat this debilitating neurological disorder.

6) PROPOSED WORK PLAN/ FORMULATION AND STRUCTURE OF STUDY

Period of Study	Achievable targets
First Year	1) Collection review, compilation of synopsis and submission 2) Collection of information of Alzheimer's disease, its development stages & Mechanism. 3) Searching & studies on naturally occurring Bioactive compounds which influences the development of Alzheimer's Disease. 4) Analysis of such a Bioactive compounds with the help of Molecular Docking tools.
Second Year	• *In Silico studies of bioactive compounds with the help ofmolecular docking tools.*
Third Year	• Compilation of data, analysis of data, submission of final synopsis and thesis

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